DANA (C. L.)

SHAKING PALSY:

A Clinical and Pathological Study, with the Reports of Two Autopsies.

BY

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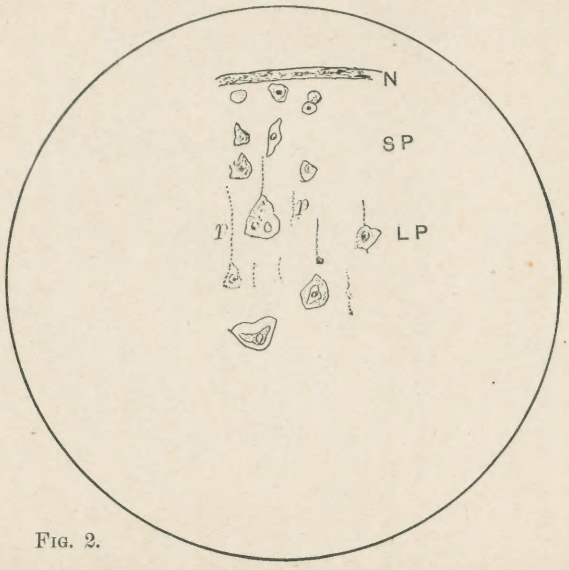

FIG. 2.

PARALYSIS AGITANS.—Brain cortex from middle of central convolutions showing atrophied cells and granular apical processes. N, neuroglia layer; S P, small pyramidal layer; LP, large pyramidal layer; *pp*, granular apical processes. (One-sixth objective).

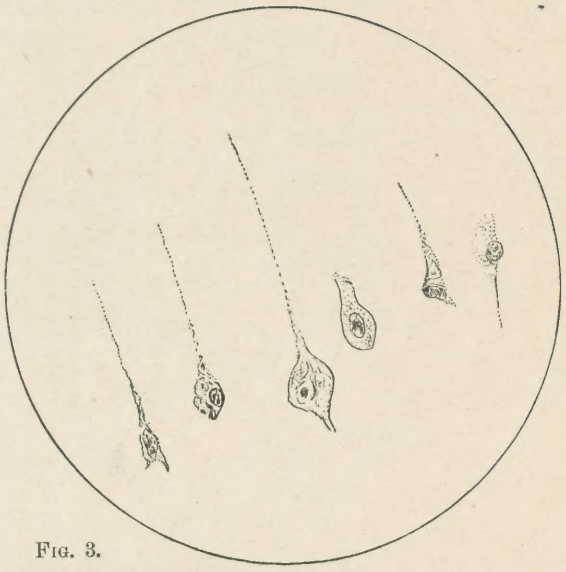

FIG. 3.

PARALYSIS AGITANS.—Brain cortex; another portion of middle of central convolutions, showing granular apical processes of large pyramidal cells, and degeneration of some of the bodies of the cells. (One-sixth objective).

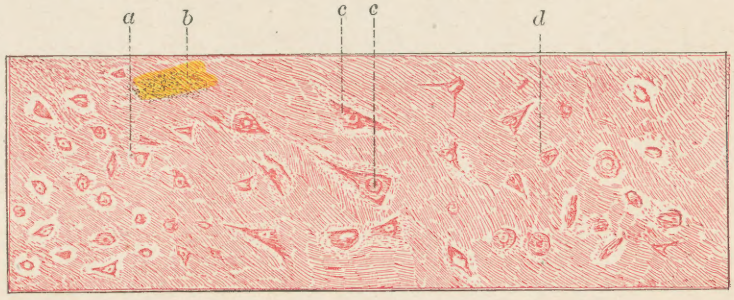

FIG. 4. PARALYSIS AGITANS.—Brain cortex, upper third of central convolutions. *a*, small pyramidal cells; *b*, blood-vessel; *c*, cells of 3rd layer; *d*, cells of 4th layer. (Drawn from one-eighth objective.)

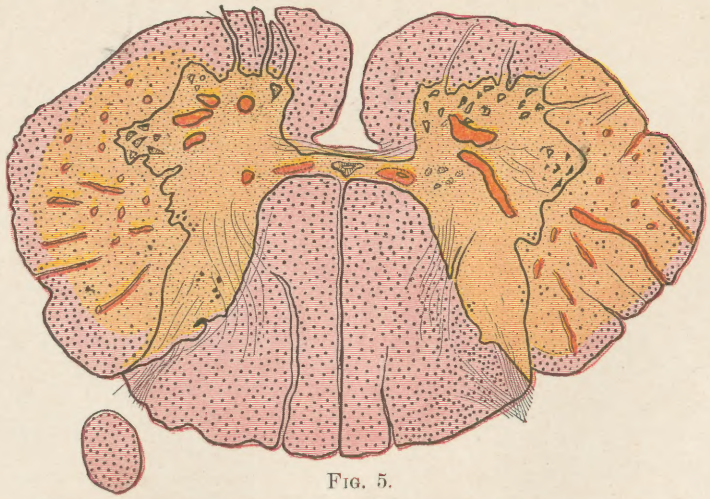

FIG. 5.

PARALYSIS AGITANS.—Level of seven inch cervical segment, showing diffuse lateral sclerosis, degenerated cornual cells, and vascular dilatation, absence of fibrillary network in anterior horns, poverty of cells in central area. Drawn from specimen, stained by Weigert's method, by Edinger apparatus. (Three-inch objective).

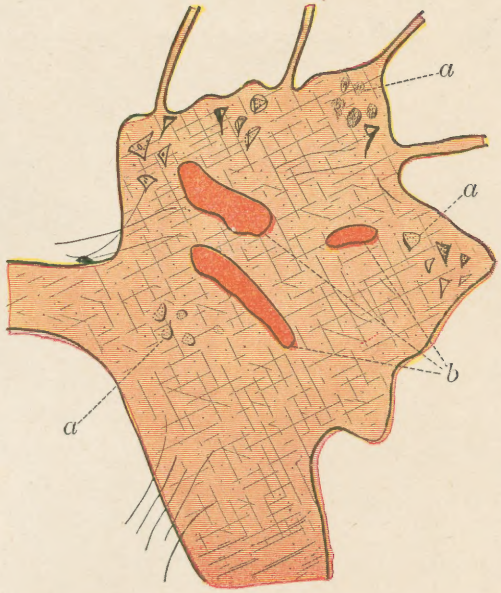

FIG. 6.

The same enlarged. *a a a*, degenerated cells, *b*, blood-vessels, or spaces left by them. (Two-thirds objective).

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SHAKING PALSY:

A CLINICAL AND PATHOLOGICAL STUDY, WITH THE REPORTS OF TWO AUTOPSIES.*

By CHARLES L. DANA, A. M., M. D.,

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Paralysis agitans is not a very rare disease. In my own experience it ranks in frequency, among chronic neuroses, closely with locomotor ataxia.† Its peculiar symptoms, its distressing and progressive course, its resistance to therapeutic measures, and finally the mysterious effacement of itself on the post-mortem table, make the study of the disease one of special interest. Yet, strange to say, very little has been done in this direction by American neurologists. I can not find the report of any autopsy made on this side of the Atlantic, though there are a number of excellent clinical studies.

* Read before the Philadelphia Neurological Society, February 27, 1893.

† Among about two thousand old people and paupers in La Salpêtrière, paralysis agitans made up four per cent. of the chronic nervous diseases, standing fifth in the list (Ordenstein).

There were twenty-two fatal cases reported in England in one year (Sanders).

Eulenberg (Berlin), among ten thousand four hundred and twenty-four nervous cases, found forty-six cases of paralysis agitans = 0·44 per cent.

O. Berger (Breslau) states that among five thousand nervous cases 0·6 per cent. were paralysis agitans. This is somewhat less than the percentage in my own experience, which is about one per cent.

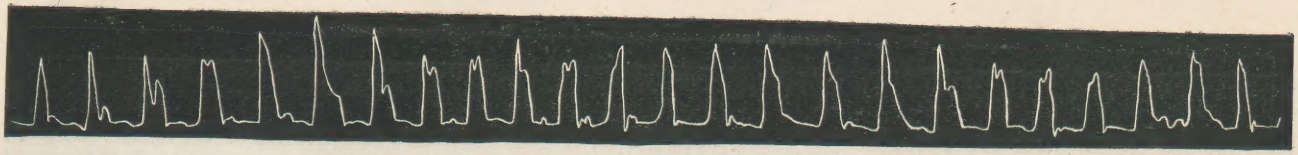
While the larger part of my remarks will be devoted to the pathological aspect of paralysis agitans, I wish first to call attention to certain clinical phenomena which are, I think, fundamental, but which are not usually very much emphasized.

CLINICAL.

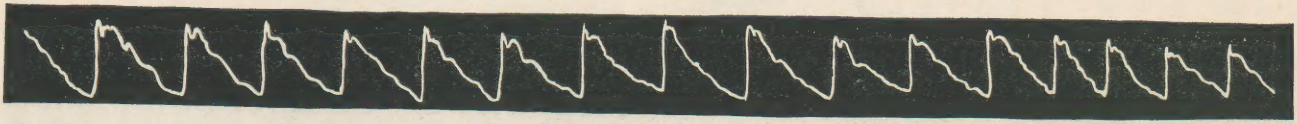
We all know that the dominant symptoms of the disease are tremor, rigidity with contractures, a slowness in initiating muscular movements, sensory and vaso-motor disturbances, and terminal paralysis.

Among these symptoms I want to recall to you first the peculiar hitch in volition, so to speak, which is so characteristic, and which I believe gives us some clew to the seat of the trouble. The patient, when asked to stand up, apparently makes the effort; his will, or I had better say here, his cortical centers work; he is conscious of effort, but the muscles do not respond. Somewhere between the cortex and the muscles the impulse is checked momentarily, as though a stream were temporarily dammed up, or a door were found stuck in the face of a man who had his hand on the knob. Having once got started, the movements are made with a fair degree of readiness and strength. But there is a block slipped into his motory mechanism every now and then. There is a hitch in it also when he attempts a new set of movements. If walking, he must come to a full stop before he can turn a corner. The automatic movements of walking or running, once initiated, pass beyond his control for a moment. There is something which cuts off the governing mechanism. Hence the slowness, awkwardness, abasia, and festination of this disease. These, which we may call the "hitch symptoms," are very curious and will be referred to later in considering the pathology.

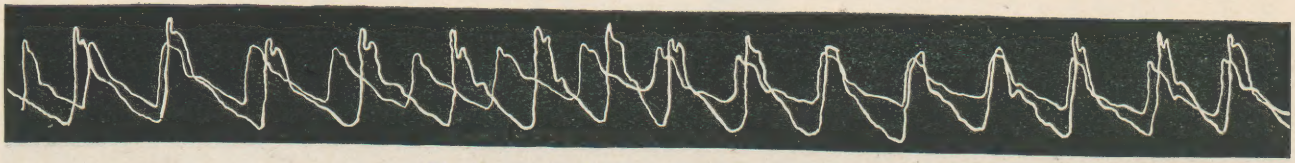
A second class of phenomena which I think deserve more attention than it has received, is that pertaining to the vaso-motor system and the blood. Very soon, often within six months of the inception of the disease, there appears a peculiar flushing of the face which gives to patients, along with the facial rigidity, a most characteristic physiognomy. There is apparently also an increase of vascularity in the skin which causes sensations of heat and fever;



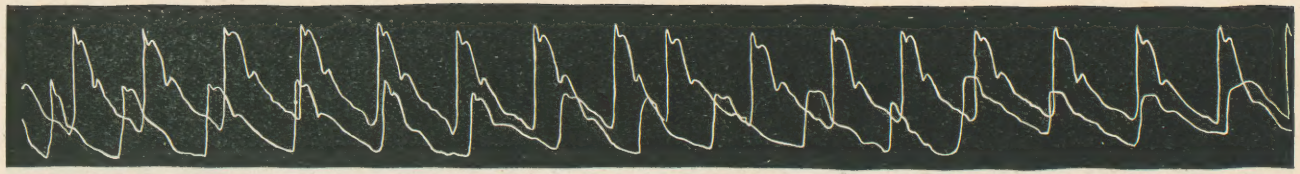
I.—D., male, aged forty-five ; duration, seven years.



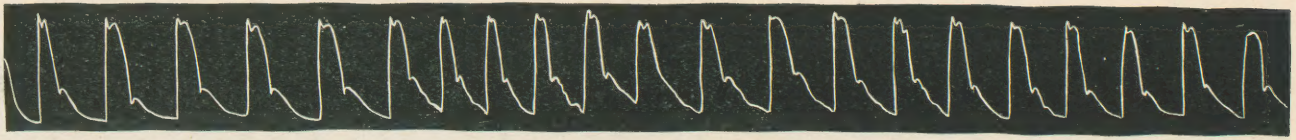
II.—Radial pulse, paralysis agitans. J. C., male, aged forty-six ; duration, six years.



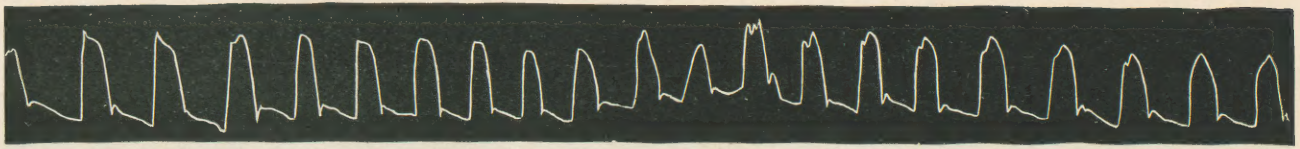
III.—K., male, aged fifty-seven ; duration three years.



IV.—Same case.



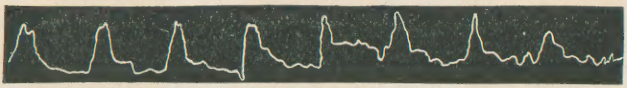
V.—F., male, aged seventy-five; duration, fifteen years; not advanced.



VII.—H., male, aged eighty-six; duration, three years; advanced stage, very senile.

the sudoriferous glands are stimulated. The increased vascularity affects the muscles, irritating the muscular nerves and causing the fidgets and restlessness so commonly observed.

A study of the pulse will show that it is at first feeble and soft; later it is full, rather tense, and sometimes a little quickened. I have made a number of sphygmographic tracings which I submit to you here. These show an unusual amplitude of the curve, with evidences of considerable vascular fullness. They resemble the sphygmograms of arterial fibrosis, but there is a weaker percussion wave indicating distended or dilated vessels. The patients, however, do not suffer from throbbing or bounding feelings or from palpitations. This is because the heart is not hypertrophied or overactive, but, if anything, is less strong than normal.



VI.—Haustm., male, aged eighty; duration unknown: case advanced and senile.

I believe it to be shown that we have in this disease all the evidences of a pretty general vaso-motor paralysis. This affects the skin and muscular systems, the spinal cord and nerves, perhaps some of the abdominal viscera, but not, as I shall show later, the cerebral hemispheres or cerebellum.

I would remind you in this connection that occasionally tachycardia occurs.

There is a third class of symptoms which I believe of essential importance: it is that which includes the disturbances of the blood and of metabolism. In a certain proportion of cases of shaking palsy attacks of purpura hæmorrhagica occur. I have a patient who has an attack every one or two years, each attack lasting several weeks. In other cases glycosuria is present and the amount of sugar may be considerable. In some cases there is an excessive discharge of phosphates.*

* While Cheron (*Le Prog. méd.*, 1877, No. 48) states that there is polyuria and phosphaturia in this disease, Gürtler (*Archiv f. Psych.*,

Through the kindness of Dr. Thomas S. Southworth, of this city, I have been able to have made very careful examinations of the blood of two typical cases of paralysis agitans—one in an early and one an advanced case. The corpuscles were counted, the hæmoglobin measured, and the staining reactions made. The results are incorporated here:

Case I.—J. H. T., male, aged forty-three; duration two years.

Fresh Blood.—Red cells of good color and thickness. Cells vary slightly in size, with some tendency to oval form. Average of good size; some large cells, no small ones. Hæmoglobin, ninety-one per cent. Reds, 4,850,000 per c. mm. Whites, 4,700 per c. mm. Ratio white to red, 1 to 1,030.

Stains.—Lymphocytes..... 28 per cent.;
Large uninuclear leucocytes... 6 per cent.;
Transitional form..... 4 per cent.;
Multinuclear leucocytes..... 62 per cent.;
Eosinophilous cells..... 0 per cent.

Diagnosis.—Very fair condition of the blood, the chief variations from normal being absence of eosinophilous cells.

Case II.—J. C., male, aged forty-six; duration six years; walking stage, but great tremor and pain.

Fresh Specimen.—Red cells light in color, fair size and shape; average somewhat smaller than usual; cells vary somewhat in size; show less resistance; crenate rather quickly. Some oval cells. Hæmoglobin, seventy-five per cent. Reds, 5,216,000 per c. mm. Whites, 4,700 per c. mm. Ratio white to red, 1 to 1,110.

Ehrlich Stains.—Lymphocytes..... 18 per cent.;
Large uninuclear leucocytes.. 1 per cent.;
Transitional form..... 2 per cent;
Multinuclear leucocytes..... 77 per cent.;
Eosinophilous cells..... 2 per cent.

Diagnosis.—Anæmia of chlorotic type; lessened percentage of hæmoglobin, and decreased resistance of red cells.

Finally, there is another very dominant class of symptoms, and these are the sensory. The disease is not very rarely preceded by a sciatica. Neuralgic and rheumatic pains and distressing sensations of heat and cold are usually

Bd. xiv, 1883), Ewald (*Berlin. klin. Woch.*, 1883, Nos. 32 and 33), and Hüber (Virchow's *Archiv*, 108, p. 52), do not find any special anomalies.

present during a good part of its course and add greatly to the patient's sufferings.

PATHOLOGICAL.

I now come to the subject of the pathological anatomy of the disease.

Below is a list of the authors who have reported cases and autopsies of paralysis agitans or diseases with symptoms resembling it:

1. Parkinson, 1817. *Essay on Shaking Palsy*, London. Sclerosis in pons and medulla.

2. M. Hall. Sclerosis of the pons and corpora quadrigemina.

3. Stofella, 1861. *Wiener Wochenblatt*, xvii, 37. Atrophy of brain with secondary degeneration about the ventricles.

4. Oppolzer, 1881. *Wien. med. Woch.* Sclerosis in the medulla.

5. Skoda, 1862. *Wien. med. Halle*, iii, 13. Sclerosis of the walls of the ventricles; softening of the pons, medulla, and parts of the cord.

6 and 7. Ordenstein. *Thèse de Paris*, 1867. Two cases. First case: duration, thirty-four years; brain normal; cord, some induration and atrophy; "rarefaction" of nerve fibers; nerves normal. Second case: female, aged fifty-eight; duration, twenty years; softening of the pons and cerebral peduncles (specimen badly preserved).

8. Leyden, 1864. Sarcoma in left optic thalamus and compression of pons.

9. Petraeus, 1863. *Hospitals-Tidende*, No. 41, 1861.

10. Virchow. Osteoma in left optic thalamus.

11. Meschede, 1870. Virchow's *Archiv*, Bd. l, p. 297. Heteropia and sclerosis of cord. A case of multiple sclerosis in a boy.

12. Bourillon, 1870. *Gazette des hôp.*, Nos. 50, 51. A case of multiple sclerosis.

13, 14, and 15. Joffroy, 1871–'72. *Arch. de physiologie*, vol. iv, p. 106. Three cases. Brain not examined.

16. Ball, 1871. Case cited by Joffroy, *loc. cit.* Brain not examined.

17. Murchison and Cayley, 1871. *Trans. of the Lond. Path. Soc.*, xxii, p. 24 (described later).

18. Meynert, 1871. *Wien. med. Presse*, p. 647. A case of general paralysis with symptoms of paralysis agitans; lesion in the corpus striatum.

19. Chvostak, 1871. *Wien. med. Woch.*, Nos. 37–39. Paralysis agitans with atrophy of extremities of left side. Intentional tremor. Sclerosis of right temporal lobe and Ammon's horn. Cord and nerves not examined.

20. Leyden, 1876. *Arch. f. Psychiat.*, Bd. vi, p. 293. A case of chronic atrophic paralysis (with paralysis agitans), chronic interstitial neuritis with myositis, atrophy, and lipomatosis. Atrophy of left anterior horn of lumbar swelling; vascular disease in the neighborhood.

21. Westphal, 1876. *Charité-Annalen*, Bd. iv, p. 361. Nothing found. Brain not examined; no details.

22. Fr. Schultz, 1876. Case of tremor of left arm and hand; no history. Post mortem showed multiple sclerosis or disseminated myelitis.

23. Rosenthal. Quoted by Eulenburg. Softened focus in medulla.

24. Leubuscher. A case of fibrous tumor of the pons.

25. Dowse, 1878. *Trans. of the Lond. Path. Soc.*, xxiv, p. 17 (described later).

26. Herterich, 1879. *Dissertat. Würzburg.* Sclerotic focus in spinal cord and in medulla (described later).

27. Luys, 1881. *L'Encéphale*, i, p. 649. Cells of pons twice normal size—*i. e.*, 40 to 50 μ in diameter instead of 20 to 25 μ.

28 and 29. Dubief, 1881, Paris. Essai sur la nature des lesions dans la maladie de Parkinson; two cases (described later).

30. Raymond, 1883. *Gaz. méd. de Paris*, p. 409.

31. Carderelli, 1883. *Riv. clin. e terap.*, 1883, v, p. 172. A case of cervical myelitis.

32. Heimann, 1888. *Ueber Schüttellähmung.* Autopsy by Oppenheim negative; no details; nerves and muscles not examined.

33. Von Sass, 1891. *St. Petersburg. med. Woch.*, p. 165 (described later).

34, 35, and 36. Koller, 1891. Virchow's *Arch.*, Bd. cxxv, p. 287. Three cases (described later).

37. Borgherini, 1891. *Rivista sperim. de Frenalvii*, vol. xvii, p. 26 (described later).

38. Wienskowitz. *Dissertation Breslau*, 1883, p. 58. Duration five years. Vessels at base of brain atheromatous and dilated. Brain normal. Cerebral and spinal meninges normal. Sarcomatous tumors on the cauda equina, right side, just below lumbar swelling. No microscopical examination.

39. Kuhne. *Dissertation Berlin*, 1872. Male, aged forty-eight; duration, four years. No change, microscopical or gross; no details.

40 and 41. Bauer, J. *Ann. d. städt. allg. Krankh. zu München*, 1878, i, 134. Two cases. Atrophy of brain and sclerosis of cord. Paper inaccessible to me.

42. Demange. *Rev. méd. de l'Est.*, Oct. 15, 1879. Slight sclerotic changes in the anterior and lateral columns; periependymitis and subinflammatory changes in posterior nerve roots and columns of Goll and Clark.

43 and 44. Teissier. *Lyon méd.*, 1888, p. 351. Two cases. Diffuse sclerosis of lateral columns; no details.*

A study of these cases will show that after the original description of the disease by Parkinson in 1817 practically no pathological studies were made of it until 1861 and 1862.

* Since this was written three more autopsies have been reported by Ketacher (*Zeitscher f. Heilkunde*).

Under the stimulus to pathology given by the Vienna school, a number of autopsies were made, but the results were of little value. The disease was not sufficiently known to be surely recognized, and the microscopical examinations were very incompletely made.

In the next decade, when Charcot had taught the profession to distinguish shaking palsy from coarser organic disease, many more cases began to be reported. The results, however, were still reported negative, or else it was found that a mistake in diagnosis had been made.

In the last six years some very carefully examined cases have been published, and I find that in proportion as these examinations have been minute and thorough they begin to agree with each other and the negative character of the findings to disappear.

I do not wish to appear arbitrary, but it is my opinion that out of the forty-four reports of autopsies in thirty-nine cases, nearly all of which I have read in the originals, only fourteen reports have any scientific value whatever. In all the other cases, so far as I can learn, the diagnosis was wrong or the examination was incomplete. For example, Charcot states that he has examined the cords in three cases and found nothing. This is all he says. Westphal reports a case in which he says he found nothing, but he gives no details and he did not examine the brain. Heimann, in a graduating thesis, 1888 (*loc. cit.*), reports a case in which the autopsy was made by Oppenheim with negative result; but here we have only this bald statement.

The cases which merit study by virtue of the fact that the disease was evidently diagnosticated during life, and the central nervous system carefully preserved and examined by modern methods, are the following: Three by Joffroy, one by Dowse, one by Murchison, one by von Sass, three by Koller, one by Borgherini, two by Dubief, one by Teissier, one by Ordenstein—total, fourteen.

Of these fourteen, the cases of Dubief, von Sass, Koller, and Borgherini are much the most valuable. I will, however, give some details of them all.

Joffroy. Case I.—Woman, aged forty-seven; duration of disease, six years. Brain: arteries not atheromatous; no microscopical examination. Spinal cord: central canal filled and

distended, amyloid bodies, pigmentary degeneration of the cranial cells. Medulla: some connective-tissue proliferation in the neighborhood of the columns, pigmentary degeneration of nuclear cells.

Case II.—Female, aged sixty-seven; duration, eight years. Brain not examined. Cord: central canal dilated and filled with degenerated cells; amyloid bodies in cord substance; cranial cells show pigmentation and atrophy with loss of processes; walls of vessels dilated and surrounded by dilated perivascular spaces—in other words, an appearance of congestion.

Case III.—Female, aged sixty-eight; duration, over ten years; mental complications in last two years. Brain not examined. Cord and medulla presented much the same appearance as in Cases I and II. A small sclerotic patch was found in the lower part of the fourth ventricle.

Dowse and Kestevan. Case I.—Female, aged fifty-two; duration of disease, twelve years. Weight of brain, fifty-three ounces; arteries slightly atheromatous. There is described a so-called fuscous or granular degeneration of the cells of the corpus dentatum and of the folia of the cerebellum. The corpora striata were honeycombed with a miliary degeneration; slighter changes were found in the optic thalamus. Cord: there was a sclerosis of the periphery of the cord, especially over the posterior and right lateral columns, also a colloid degeneration in this neighborhood. The cells of the anterior horns showed degenerative changes. The vessels were much more dilated and even sacculated with large perivascular spaces. In the medulla the cells of the olivary body were pigmented and degenerated. The nucleus of the ninth nerve showed degeneration, and also that of the eighth. The general condition seems to have been one of quite widely extended congestion of the central parts of the spinal cord and medulla, with very marked degenerations affecting the cells of both the brain and medulla and spinal cord.

Murchison and Cayley. Case I.—Male, aged twenty-one; duration, twelve years. Death due to typhus. Brain not examined. Central part of the cord completely transformed, filled with leucocytes extending into and occluding the central gelatinous substance; strong vascular injection of the cord and slight blood extravasations due probably to typhus. There was a thickening of the periphery of the spinal cord and connective-tissue increase throughout the substance of the cord, especially of the cervical and dorsal parts and in the posterior columns.

Von Sass. Case I.—Female, aged twenty-one; duration, twenty years. Brain and medulla not examined. The cord showed thickened arteries, corpora amylacea, increase of connective tissue throughout its substance. Central canal in many

places obliterated; proliferation of the cells of the ependyma. A small focus of sclerosis was found in the median part of the floor of the medulla. Peripheral nerves: a proliferation of connective-tissue sheaths with increase of nuclei; some degeneration of fibers; vessels thickened. Diagnosis here was made of a chronic interstitial neuritis. Muscles: the fibers were smaller, striation indistinct with increase of nuclei. Diagnosis here was made of chronic myositis similar to that found, however, in old people, only more marked.

H. Koller. Case I.—Female, aged seventy-six; weak, bedridden, and demented at the time of death; duration of disease not stated.

Case II.—Male, aged sixty-nine; no history given or known.

Case III.—Male, aged seventy-one; duration, seven years; cause, trauma with fracture of clavicle. The changes found post mortem in these three cases were described together by Koller, and it is inferred that they were all more or less present in each case. Brain showed congestion and œdema; the arteries were moderately thickened but not atheromatous. In one case there was a small focus of softening in the left hemisphere near the posterior end of the caudate nucleus; a second smaller focus was found beneath the cortex in the occipital lobe. In another case the brain was not examined, and in a third case the findings in the brain were negative. Spinal cord: there was thickening of the pia mater, especially in the anterior region; the posterior and lateral columns showed a considerable proliferation of connective tissue with numerous dilated vessels. The sclerosis in these areas seems to have started from the neigh borhood of the blood-vessels. There is a periarteritis described by this author on which he lays very much stress. The motor cells showed some pigmetation and there was generally a granular, often coarsely granular, degeneration. Some change in the myelin sheaths of the nerves was also noted. On the whole, the morbid process seemed to affect the vessels and connective tissue most seriously. Koller describes three grades of changes discovered in the cords. First grade, the perivascular thickening; second, proliferation of neuroglia tissue; third, proliferation of nuclei. Koller lays, as stated, much stress upon the periarteritis, which he seems to think to be somewhat characteristic, and also affirms his belief that there is an extensive proliferation of connective tissue originating from the blood-vessels and affecting specially the lateral and posterior columns and the central parts of the cord. Pigmentary and other degeneration of the cells were also observed. He notes furthermore a proliferation of the endothelium of some of the blood-vessels and finds some of them stopped up with hyaline masses. He looks

upon paralysis agitans as a process half way between senility and multiple sclerosis—a diffuse and perivascular rather than a multiple sclerosis.

Borgherini.—For a translation of the report of this case I am indebted to my friend Dr. Joseph Collins.

Patient died of pneumonia. Post-mortem showed the lesions of that disease and, in addition, a widespread arterio-sclerosis.

Pieces of the cerebrum, cerebellum, medulla, spinal cord, vagus, the median, the anterior tibial, one of the cervical ganglia, and some muscular fibers of the biceps were taken for microscopical examination (preserved in Müller's fluid). The microscopical examination of the brain revealed a moderate alteration of the capillary vessels, the walls thick and rich in nuclei, the lumen enlarged, and the lymphatics and the perivascular spaces likewise enlarged. There could be seen small connective-tissue fibrillæ starting out from the capillaries, shooting into the surrounding nerve tissue, and a certain number of amyloid corpuscles were deposited in the perivascular lymph spaces alongside these connective-tissue buddings. The small ganglionic cells and the nerve fibers seemed to be normal. In the cerebellum the same conditions were noticed as in the brain. The changes in the pons were very conspicuous, and they affected the vessels as well as the nerve matter. The vascular lesions were of the same nature as those of the brain, with the exception that here they were more marked. The vessel walls were very thick; the smaller ones presented some aneurysmal dilatations; the lymphatics and perivascular lymph spaces were very ample. At the periphery, under the pia mater, the whole external surface of the piece was covered with a connective-tissue layer, and this sent fibers into the substance of the tissue (the pons). The ganglionic cells of the pons were pigmented, their processes stunted, their general outline deformed and surrounded by large perivascular lymph spaces. The ependyma of the fourth ventricle appeared thickened; the roof appeared normal, with some epithelial thickening; with large nuclei and overgrowth of the capillary vessels. The gray substance on which this granular substance rested was atrophied; numerous vacuous places could be seen and many large capillary vessels. The cellular substance of the nerve matter was pigmented, and in some places this was so extensive as to render the protoplasm opaque. Such atrophy could be observed, with a very little difference of degree, principally in the nuclei of the vagus, the glosso-pharyngeal, the facial, and motor oculi. Scattered throughout the atrophied gray substance, in the floor of the fourth ventricle and principally around the vessels, were found numerous large amyloid corpuscles. The restiform bodies appeared normal.

In the medulla the periphery of that body presented similar changes to those noticed at the periphery of the pons. Large prolongations of connective tissue went in from the surface to the medulla and principally into the pyramidal tracts. The neuroglia appeared everywhere thickened. The vascular changes were the same as mentioned in the pons, and there was seen considerable rarefaction of the nervous substance (enlargement of the perivascular lymph spaces), particularly in the region of the external arciform fibers and in the region of the inferior olives. The ganglionic elements of the olives and the interolivary bundles seem normal. In those portions of the medulla where the rarefaction already spoken of existed there was to be seen remarkable enlargement of the smaller blood-vessels and with thick walls. The neuroglia had a sort of fibrous look, and the amyloid corpuscles were here most abundant.

In the spinal cord the changes were most noticeable in the cervical and upper dorsal portion. The periphery of the cord was encircled by a connective-tissue ring; the neuroglia was thickened and filled with nuclei; in the gray substance, particularly in the posterior horns, there were numerous greatly enlarged blood-vessels, and the nerve processes seemed short and broken. The central canal was encroached upon by numerous nuclei. The ganglionic cells were fairly well preserved. In the spinal roots several atrophied fibers existed. The vagus, median, and external tibial presented prominent alterations, consisting of atrophy of several of the nerve bundles, with increase of the connective interstitial tissue and of alterations in the capillary vessels. In the cervical ganglion examined the atrophy of the cellular elements was quite well marked; the blood-vessels showed marvelous examples of miliary aneurysms; the interstitial connective tissue was abundant. The muscular fibers of the peronei did not appear much altered, but those taken from the biceps appeared atrophied and excessively pigmented. The fibers were thin and broken down, the perimysium thickened and filled with nuclei and other evidences of degeneration (myositis).

The histological examination proves, before anything else, that there were prominent alterations in the central as well as the peripheral nervous system, and in the sympathetic as well as in the muscles. The most prominent lesions were those affecting the blood-vessels; but, at the same time, groups of nervous elements were also altered, principally in the gray substance around the fourth ventri-

cle and in the gray matter of the spinal cord in its upper portions. The white substance was not entirely spared, but it appeared much less affected. The alterations in the sympathetic system were very conspicuous, while in the cerebrum and cerebellum the changes were not so conspicuous; they were intensified in the pons and medulla and decreasing as we passed into and down the spinal cord.

From this point the paper is concerned with a justification of his interpretation of the lesions found, and the dependence of the symptoms upon them.

He believes that greatest stress should be laid on the vascular changes.

He says later that he truly believes the pathogenesis of shaking palsy is the alteration of the capillary vessels and the small arterioles, and this is followed by secondary changes of a degenerative nature in surrounding parenchymatous cells.

Herterich.—Female, aged sixty-six; duration, ten years. Disease followed typhoid; autopsy not made till thirty-six hours after death. It was noted that at the time of her death the temperature gradually rose from 37° to 40·4° C. She had some disturbances of speech and dysphagia at this time. Eight hours after death the temperature was 39° C. There was a very strong rigor mortis. At the upper end of the cervical cord there was seen a heteropia (?) of the gray matter; in the cervical cord there was a yellowish spot of fatty degeneration in the left anterior horn; lower down in the cervical swelling some degeneration of the left lateral column and intermediate gray matter was noticed; lower down still were slight traces of sclerosis in the left anterior and right posterior columns. In the lumbar cord the gray matter at the periphery of the anterior horn was yellowish. There was a general degeneration of the floor of the fourth ventricle 2 mm. deep. There was a thickening of the ependyma, and there was a softened focus in the pons extending into the left crus. No microscopical examination. Commentary: It is evident that this was a complicated case and not one of pure paralysis agitans.

Dubief.—Dubief reports two cases which died of intercurrent maladies—namely, of cardiac disease and cancer, in a comparatively early stage of paralysis agitans; hence he thinks his examinations of special importance.

Case I.—Female, aged fifty-seven; duration, six years. Patient had had several attacks of acute rheumatism while suffering from her palsy.

Post-mortem.—Spinal cord: There was a thickening of the pia and distention of the central canal, with thickening of the ependyma. The thickened pia mater produced a peripheral sclerosis irregularly distributed and extending into the substance of the cord along the septa, forming a kind of diffused sclerosis. There were amyloid bodies noticed around the blood-vessels. The cells of the anterior horns were strongly pigmented; they also showed a peculiar reaction to stains, evidencing a degeneration of the protoplasm of the cell substance; only the nucleus and part immediately around it would take up the carmine well. The processes were varicose and imperfect. Dubief describes a swollen condition of the axis cylinder of the nerve fibers in the cord. Similar lesions to the above were noticed in the pons and medulla, but they were less advanced here. Brain and cerebellum normal. The nerves of the brachial plexus showed great increase of connective tissue.

Case II.—Male, aged sixty-seven. Patient was a very hard drinker, sometimes taking five litres of wine a day. Seventeen years before his death he had had an attack of sciatica. His tremor began fifteen years before death; he died of cancer. The spinal cord of this case presented lesions somewhat like those in Case I. In the brain he found fourteen small echinococcus cysts of about 1 c. c. capacity. They were distributed over the cortex; one was posterior to the right optic thalamus, one in the head of the caudate nucleus. The arteries were atheromatous, the membranes thickened. Dubief thinks that paralysis agitans has lesions of senility, only differing from those of senility in their exaggeration and their precocity.

The Author's Cases:

Case I.—Regina S., Germany, married, aged fifty-six, admitted to Montefiore Home in September, 1887. About two years before admission, while doing some work in a house, she was much frightened by the breaking out of a fire in the store in front. At the time she experienced a sensation of weakness in the back. Several days later she noticed that there was a tremor in the left hand. This in time extended to the whole arm, then to the right hand and arm, afterward to the left lower extremity, and finally to the right. In the lower extremeties the tremor has been very mild. She has suffered much with pain of the small of the back and for the past year has not been able to straighten the same. Also finds that the left side is much weaker than the right, so that she can not bear her weight on it in walking. Lately her feet and ankles have been swollen in the evening. At times she has much pain in the left shoulder. Appetite is fair; bowels regular; patient is fairly nourished; tongue slightly coated. Walks and stands with a marked stoop and favors

the left side. Grasp of left hand much weaker than right, which is itself not very strong. Muscles of arms and shoulders have a much firmer feeling than normal. Pulse fair. Heart and lungs negative. No œdema. Urine negative.

Treatment.—House diet. Hyosc. hydrobrom., gr. $\frac{1}{400}$, t. i. d. after meals. Rub back with chloroform liniment, aconite, and alcohol.

October 2d.—Pain in back is somewhat easier. Slight œdema is noticeable about the ankles in the evening. Is able to be about, but favors the left leg very much in walking. Is able to eat alone, but can carry food to mouth only very slowly and with some difficulty. Tremor of left hand more marked than right, but neither is very much accentuated.

13th.—Condition remains about the same. At times complains of much pain in right shoulder and in the left ankle. Appetite is fair; bowels regular. Omit hyosc. hydrobrom. Potass. brom., gr. xv, t. i. d. Sol. menthol extern. p. r. n.

24th.—Occasionally complains of headache, always frontal, and during the latter part of the day. Thinks she is somewhat stronger. Can go up and down stairs without difficulty. Potass. brom., gr. xx, t. i. d.

November 10, 1887.—Is fairly comfortable. Continues occasionally to complain of pains in back, shoulder, and left leg. Walks very much stooped.

22d.—Appetite is rather poor. Sometimes complains of pains in the epigastric region; relieved by a mustard plaster.

Omit potass. brom. Tincture gentian co., ʒ j., half an hour before meals.

December 7th.—Appetite is improved. Patient is becoming more helpless and has more difficulty in feeding herself. Left arm is quite stiff and almost useless. Continues to have pains in various parts of the body occasionally. Omit tincture gentian. co. Potass. brom., gr. x, t. i. d.

January 10, 1888.—Is becoming more and more helpless. Frequently has pain in shoulders and arms. Some œdema of feet and legs, more pronounced on left side than on right. Appetite is good; bowels regular.

February 21st.—Continues to have much pain in shoulders at times. Appetite is poor. Occasionally has intestinal pain after eating. Also complains of headache occasionally, which is relieved by application of menthol solution.

March 12th.—General condition remains about the same.

29th.—Is unable to feed herself both on account of tremor and on account of the slowness with which she must carry articles of food to her mouth. At times has much pain in small of back, so that she must go to bed.

June 20th.—Patient's strength remains good. Is able to go up and down stairs, although with some difficulty. Appetite is very fair. Eats very little meat. Omit potass. brom.

August 17th.—Suffers much from the heat and flies. When latter settle on her face she is unable to drive them away on account of difficulty she has in moving her arms.

September 20th.—On account of cooler weather has been much more comfortable for the past three weeks. Occasionally complains much of abdominal cramps; relieved by mustard plaster or tr. zingib., 3 ss.

Fig. 1.—Paralysis agitans, late stage.

October 20th.—Is quite helpless, sitting in the same position in her arm-chair the greater part of day. Usually is quite cheerful.

November 15th.—General condition remains about the same.

December 4th.—Has lately complained much of cramps in abdomen, which are relieved by simple enema. After sitting up a long time has pain in small of back. General condition remains about the same.

January 1, 1889.—Is unable to pass urine without the aid of hot applications to lower abdomen.

15th.—Has vomited several times lately. Still complains of cramps in abdomen. Bowels are sometimes loose, sometimes constipated. Still trouble in passing water. Potass. acet., gr. xx, every four hours. Strychn. sulph., gr. $\frac{1}{60}$ t. i. d.

Patient became gradually weaker and died of exhaustion in March, 1889, five years after onset of her malady.

Autopsy, made by Dr. Rosenthal, to whom I am indebted for the foregoing clinical notes.—Notes of the examination of the organs other than the brain and cord were not obtained, nor have I any records of the fresh appearance of these latter organs. The brain and cord were hardened in Müller's fluid. Portions were taken and stained in carminate of sodium by Weigert's method, also in Delafield's hæmatoxylon, aniline blue, Congo red, osmic acid, and carmin.

The central convolutions of the right hemisphere were divided into ten equal parts, and sections were made from each of them. Sections were also made of the internal capsule, basal ganglia, pons, medulla, cerebellum, eight levels of the cord, and of the cauda equina. No portions of the muscle or nerve were obtained. The sections were examined with $\frac{2}{3}$-, $\frac{1}{6}$-, and $\frac{1}{12}$-inch objectives.

Motor Cortex.—The meninges were not thickened; neuroglia layer normal. There is considerable increase in capillary vascularity; some dilatation of vessels; their walls are not notably thickened. No evidence of exudation or perivascular dilatation. The neuroglia tissue is not much increased.

In the *paracentral lobule* there is considerable vascularity, a good many dilated and empty vascular spaces. This is not observed in all parts. Some of the nerve cells are apparently normal, but the pericellular spaces of the angular (second) and pyramidal (third) layer are large and dilated. In one area only I find bad cells with atrophied processes, bodies divided as though going to pieces, nuclei indistinct.

In some sections of the *upper* and *middle* motor cortex I find cells which have lost their sharp contour. The apical processes seem granular, are pale, and stain badly. The bodies have apparently two nuclei, and look as though they were breaking up. In some cases the process seems dropping off and the cell falling to pieces (Figs. 2, 3).

In other sections there can be seen numbers of fine granular

apical processes which seem to have lost their bodies, but remnants of the latter are to be found on careful examination. It gives the field the curious appearance of a number of minute worms (Fig. 2).

The lower third of the motor convolutions shows reasonably normal cells, vessels, and neuroglia.

The whole of the motor area, when compared with that of a case of chorea and one of multiple neuritis, shows rather more vascularity, more neuroglia nuclei, and rather poorer cells.

The fiber network of the cortex, as shown by osmic acid and Weigert stains, shows nothing abnormal.

Internal capsule is normal.

The optic thalamus shows a very fine capillary injection (as in normal brains), no connective-tissue proliferation, no extravasations or exudates; cells normal, so far as I can tell. There is perhaps an intenser congestion than normal in central parts and at the boundary between the thalamus and the capsule. Some large distended vessels are seen in these parts.

Cerebral peduncles (crus and tegmentum), *substantia nigra*, *red nuclei*, *corpora quadrigemina*, *pons nuclei*, and *pyramidal tracts* normal.

Aqueduct of Sylvius.—The epithelial lining is in parts gone, but is mostly in its place. It is covered in parts with several layers of proliferated round cells.

Cranial Nuclei.—The third nerve: The cells are normal, but occasionally there is a large pericellular space. There is an excess of neuroglia nuclei and connective tissue in the neighborhood. The third nerve fibers are normal.

Sixth nerve nucleus normal.

Seventh: Cells are granular, no nucleoli; many processes gone; nerve network stains badly; some cells are pigmented, and pericellular spaces large. The change is more marked on one side. The cells are very large, but not abnormally so, in my opinion. It may be these cells of the seventh nucleus which Luys refers to as the hypertrophied cells of the pons.

The motor tracts at this level are normal. The floor of the medulla is normal.

Ninth (glossopharyngeal): This nucleus shows degeneration of cells of same kind as in tenth, but of less extent. The ascending root of the ninth and tenth (respiratory bundle) is normal.

Tenth (vagus): In the upper part of this nucleus the cells appear fairly good, but lower down many are greatly pigmented; others have lost their process, are atrophied, and shriveled up almost to simple spots of undifferentiated sub-

stance. In this part there seems to be almost a complete softening or atrophy, with cell *débris*. Here, too, one sees congestion and distended vessels just as in the cord.

Eleventh (spinal accessory): The nerve cells show great pigmentation and atrophy almost as severe as that of the vagus nucleus. The ascending root is not much affected.

Twelfth (hypoglossal): The nerve cells are apparently normal.

In the spinal cord there was a thickening of the pia mater and some proliferation of connective tissue beneath it, as described by Dubief. There was a diffuse infiltration of connective tissue in the lateral columns, involving the lateral fundamental columns (Figs. 5, 6), but not the cerebellar tracts. This was especially marked in the cervical, next in the lumbar, and least in the dorsal regions. The posterior columns were somewhat congested but not sclerosed. It was a primary connective-tissue proliferation, for the columns contained an abnormal number of arteries with thick walls and connective tissue about them. Starting from these points, it ran in among the nerve

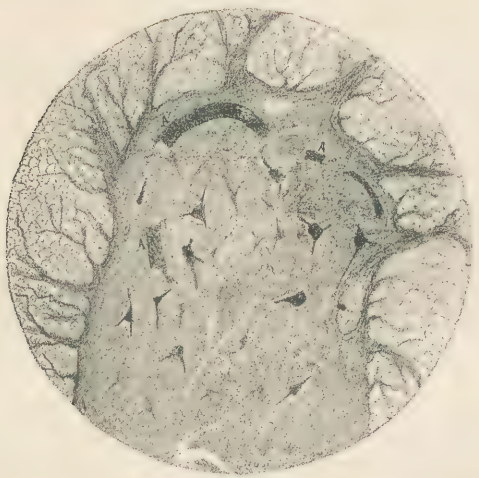


FIG. 7.—Paralysis agitans. Anterior horn of the spinal cord, showing dilated veins (upper dorsal region).

fibers, not many of which were degenerated. The central canal was distended and filled with epithelial *débris* and exudate at most levels, but not in all. The vessels of the central and anterior gray matter were numerous and distended, especially the veins. The anterior horns in particular showed a peculiar vascularity due to the presence of large distended vessels which

crept up into the field, looking like angle-worms burrowing among the cells. The cells at most levels were somewhat shrunken,* often pigmented, stained irregularly, and had lost some of their processes. The smaller cells of the central and median groups seemed especially atrophied (Fig. 8).

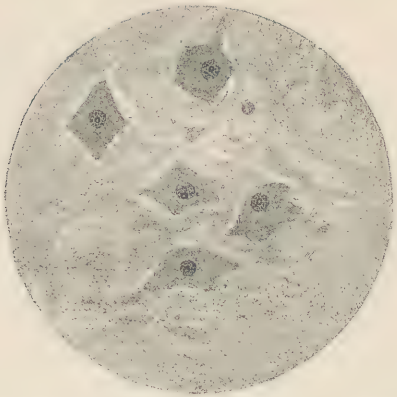


FIG. 8.—Paralysis agitans. Showing atrophied cells in the anterior horn (lumbar region).

The lumbar cells averaged $\frac{1}{600}$ inch, the cervical $\frac{1}{700}$ inch in diameter.

The blood-vessel walls were somewhat thickened, but not greatly so.

The anterior roots were congested and perforated with dilated vessels. The posterior roots were less affected (Fig. 9) In neither were there degenerated fibers. Examination of the cauda-equina roots showed nothing abnormal except a slight increase of vascularity.

CASE II.—This was the cord of a case of paralysis agitans, whose history is unknown. It was in the Carnegie Laboratory and kindly placed at my disposal by Dr. H. M. Biggs. The cord was not in the best state of preservation, and, although careful studies were made of it, I do not place much reliance on the results.

* Record of measurement of anterior horn nerve cells in spinal cord of Case I. Measurements made with stage micrometer and camera lucida in inches. In lumbar segment: $\frac{1}{600} \times \frac{1}{600}$; $\frac{1}{600} \times \frac{1}{600}$; $\frac{1}{600} \times \frac{1}{600}$; $\frac{1}{600} \times \frac{1}{400}$; $\frac{1}{600} \times \frac{1}{600}$, nucleus $\frac{1}{1200}$, nucleolus $\frac{1}{2500}$; $\frac{1}{600} \times \frac{1}{800}$, nucleus $\frac{1}{1200}$, nucleolus $\frac{1}{2500}$; $\frac{1}{800} \times \frac{1}{800}$, nucleolus $\frac{1}{3000}$; $\frac{1}{700} \times \frac{1}{700}$, nucleolus $\frac{1}{3000}$; $\frac{1}{800} \times \frac{1}{700}$; $\frac{1}{1000} \times \frac{1}{1000}$; $\frac{1}{700} \times \frac{1}{800}$, nucleus $\frac{1}{1200}$, nucleolus $\frac{1}{2500}$; $\frac{1}{400} \times \frac{1}{800}$. Cervical cord: $\frac{1}{700} \times \frac{1}{600}$; $\frac{1}{1000} \times \frac{1}{1000}$; $\frac{1}{700} \times \frac{1}{800}$; $\frac{1}{800} \times \frac{1}{800}$; $\frac{1}{700} \times \frac{1}{800}$; $\frac{1}{700} \times \frac{1}{700}$.

There was a very marked thickening of the pia mater; there was a diffuse interstitial sclerosis affecting the lateral col-

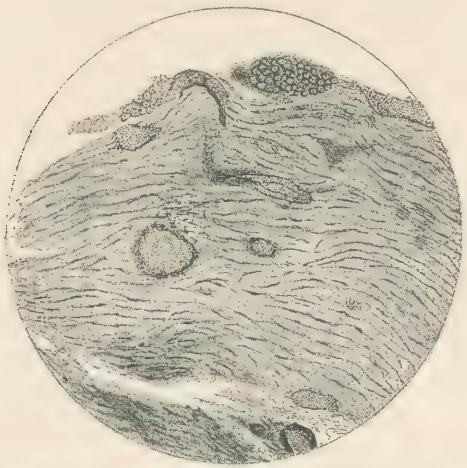


FIG. 9.—Anterior root in a case of paralysis agitans, showing congestion and dilated vessels. (⅛ objective.)

umns especially. There was congestion of the central and anterior gray matter, and slight changes in the nerve cells.

SEAT OF THE DISEASE.

With the foregoing facts before us it remains to discover whether we can draw any inferences as to the seat and character of the disease. I propose first to see whether we can satisfactorily locate the seat of the trouble in any particular part of the nervous or muscular system. There have been various theories put forth regarding this subject in the past, and I can perhaps deal with them best by taking them up seriatim and discussing them from the points of view of the pathological and clinical data now at our disposal.

Von Sass and others have suggested that the primary anatomical and pathological change is in the muscles and that shaking palsy is a kind of muscular distrophy. From this view I must absolutely dissent, for, in the first place, it is impossible to understand how the peculiar tremor of the disease could be caused by any known form of muscular disturbance. The tremor in paralysis agitans is not a

twitching, irregular, and fibrillary one, such as is seen in dying or diseased muscles or in those in which the nerve supply has been cut off, but it is a rhythmical, co-ordinated movement involving groups of muscles physiologically related. Nor can the pains, the vaso-motor disturbances, and blood changes of this disease be explained on the muscular hypothesis. Finally, it is impossible to understand how an extensive and chronic dystrophy could occur without causing some changes in the electrical reactions.

2. The idea that shaking palsy is located in the peripheral nerves and that its symptoms are produced by an irritation of them may be dismissed still more summarily. It is true that there are some changes of an irritative and degenerative kind in these parts, but direct irritation of nerves can not cause tremor, while very extensive nerve change would lead to symptoms of atrophy, paralysis, anæsthesia, and abnormal electrical reactions such as do not occur.

3. Some authors have suggested that paralysis agitans was seated primarily in the cortex of the brain, and I will confess that I was at one time inclined to think favorably of this view. But anatomical investigations uniformly show that the cells of the brain cortex are very little diseased, if at all; nor are the meningeal or vascular changes severe, even in late stages of the disorder. If the lesion were primarily here, we should certainly find some evidence of it in the terminal stage at least. Again the tremor of paralysis agitans is coarse and segmental in character, the vibrations being from four to six per second, while cortical tremors, as shown in general paresis, in ataxic and neurasthenic states, and in degenerative disorders of this part of the brain, is fine vibratile, ranging from eight to ten per second. Furthermore, a chronic cortical degeneration would almost surely lead to mental changes and disturbances, and these are very rarely present, or, if present, serious. I have seen patients whose minds were perfectly clear even during the last weeks of the disease.

4. The so-called hemiplegic or unilateral course of paralysis agitans, the fact of the temporary control over the tremor by the will and its cessation during sleep, would lead one, perhaps, to place the seat of the disease in the brain. Now, since it can hardly be in the cortex, it has been sug-

gested that the primary focus of the disorder was in the great ganglia at the base and the internal capsule. Several cases have been reported in which unilateral symptoms of paralysis agitans have been caused by tumors of the optic thalamus and corpus striatum (Leyden, Virchow). In studying the pathology of these regions, however, we find that gross diseases here never cause symptoms exactly like those of the disorder under consideration. The mobile spasms may simulate somewhat that of paralysis agitans; but the vaso-motor symptoms, the sweating, the neuralgic pains, the restlessness, and insomnia are not present. The severe symptoms such as mark the last stage of the disease would surely not occur unless there was some anatomical change in the parts in question; yet in my own sections the basal ganglia seemed to be exceptionally free from any evidence of nervous and vascular disease.

The argument that the disease must be cerebral because of its hemiplegic onset has perhaps the most force of any. I find, however, that, on careful questioning, the history of a hemiplegic course is rare. It nearly as often goes from the right to the left arm, or, as in one case of mine, from the right arm to the left leg. I can only explain the genuine hemiplegic progress by supposing that the spinal-cell groups are more easily affected on the one side than on the other.

Finally, Demange (*Rev. méd. de l'Est*, October 15, 1879) cites a case in which the tremor of shaking palsy continued after an attack of hemiplegia.*

I am led, therefore, to place the *anatomical seat of the disease in the spinal cord, medulla, and pons;* in other words, in the lowest segment of the central gray matter. There are, I believe, sufficient changes in this area to justify the belief that the pathogenic factor at work here might cause the symptoms. I would go further now and say that it is not all parts of the cord that are chiefly affected; the disease seems to be most marked in the blood-vessels which supply the central parts of the cord and the anterior horns, and next in the lateral columns, including both the pyramidal tracts and the lateral fundamental columns and lat-

* On the other hand, Parkinson, Westphal, and Grashey have reported cases in which the tremor was stopped temporarily by an attack of hemiplegia.

eral limiting layers. Finally, there seems to be some evidence of disorder in the posterior columns, though of less degree. The more or less extensive degeneration of the peripheral nerves and muscles can easily be explained as an adjunct or secondary phenomenon.

NATURE OF ANATOMICAL CHANGE.

What now are these anatomical changes? The records of the post mortems which I have read to you indicate a very decided uniformity of result in the observations of these parts. We can no longer say that paralysis agitans is a purely functional disease without any anatomical basis. This anatomical basis I believe to be essentially as follows: First, a congestion of the central and anterior parts of the gray matter of the cord with some thickening of the blood-vessels, but not very much, and some changes of the external wall of the nature of periarteritis. With this congestion and vascular irritation there occurs a proliferation of connective tissue, which especially invades the lateral columns of the spinal cord. It in severe cases affects also the periphery, producing a leptomeningitis and a zone of sclerosis surrounding the cord in a variable degree. The congestion with dilatation of blood-vessels affects especially also the anterior roots, to a less extent the posterior roots. There is degeneration of the cells of the anterior horns, which, however, occurs only late in the disease and does not affect all the cell groups. The central cells or the cells of the median and central areas, which we suppose to be more connected with vaso-motor and glandular functions, seem to be especially involved. There is also—and this is an important fact to bear in mind—a decided loss of the fiber network in the anterior horns and the central gray matter. The changes appear to involve especially the cervical and lumbar regions. Similar changes occur in the medulla and pons, but here they are less marked. Degenerative changes, however, are to be found, in many cases at least, in the cells of the nuclei of the glossopharyngeal and pneumogastric nerves. Such changes would explain the disturbances in the vaso-motor function and heart action found in the disease.

PATHOLOGY.

So much now for the anatomical basis of paralysis agitans; can we say yet what is the nature of this change? This of course is the most important question of all, for we have not by any means reached the solution of the nature of a disease by simply finding certain anatomical changes underlying it. In investigating the subject of the pathology we must necessarily approach somewhat the region of hypothesis, and I must beg your indulgence if I at this point leave for a time the firm ground of fact for the less satisfactory field of speculation. A study of the changes which have been described by authors and which I have seen myself leads me very strongly to the conviction that the process here is one that is primarily of an irritative and subsequently of an inflammatory character, and that we may speak of paralysis agitans as being a peculiar chronic and progressive inflammation of the spinal cord—an inflammation which may be more specifically characterized as a diffuse interstitial myelitis. Even this statement of the matter, however, does not include all that we want to know. There can be no irritation or inflammation without some cause, and it is perfectly understood by the pathologists of the present day that a chronic inflammatory process must be due to some irritating or toxic substance.

My own theory and belief are that paralysis agitans is due to a toxine—microbic or humoral; that this toxine circulating in the blood has an especial affinity for certain areas of the spinal cord and medulla oblongata and to a less extent of the peripheral nerves. This toxine, while at first simply of an irritating kind, such as leads to tremors, pains, and vasomotor disturbances, eventually destroys some of the parts which it at first irritates, and thus we find in the later stages of the disease a destruction of some nerve cells, degeneration of others, and a destruction and atrophy of nerve fibers and nerve-cell processes. The source of this hypothetical toxine we as yet know absolutely nothing about. There are many things in the course of the disease which lead one to think that it is allied to the substances which produce gouty, rheumatic, rheumatoid, and arthritic troubles; in other words, that it is of endogenous origin and due perhaps to

some defect in the activity of certain glands. Following a reasonably careful process of induction, we might be led to think that *paralysis agitans was not primarily a nervous but a glandular disease* in which, owing to the defect in the action of the liver, spleen, or adenoid or some other metabolic tissue, there was thrown into the blood a poisonous substance, producing the symptoms of the disease which we are studying.

The action of opium in suppressing to so great an extent many of the symptoms of the disease might be explained by the fact that opium has the power of checking glandular action and modifying so markedly tissue change. There are some reasons which lead me to venture into a still more minute and detailed theory of this disorder. We all know that a prominent and striking symptom of shaking palsy is the fact that there is a hitch or stoppage in volitional impulse, just as though there were some point between the cortex and the muscle where the nerve impulse is stopped. Now, since we know that the muscle and nerve and anterior-horn cell are healthy in the earlier part of the disease, since we know that the motor cells in the cerebral cortex and that the voluntary motor tract are not at all diseased at first, there seems to be but one place in which this hitch or stoppage can occur, and that is at the point where the terminal-end brushes of the voluntary motor tract surround and touch the anterior motor cells; in other words, the *primary lesion in paralysis agitans is perhaps a degeneration of the end brushes of the motor tract which lie about the anterior-horn cells.*

This theory, which is led to by a process of logical induction, is justified also by the fact which I have observed in many carefully stained specimens—that the fibrillary network in the anterior horns is very much atrophied and very much less distinct than in normal specimens. I have sections here in which this disappearance of the network of nerve fibers, which is always shown so beautifully in Weigert stains, is hardly present at all.

But the anterior-horn cells are surrounded not only with end brushes from the motor or pyramidal tract, but also with end brushes that come in through the posterior roots, forming in this way the anatomical substratum for

reflex action. If my theory were true, these end brushes should be somewhat affected also, and consequently reflex acts be somewhat delayed or disordered just as voluntary acts are. In several cases in which I have made a test I have found that the skin reflexes in cases of paralysis agitans are absent or are imperfectly brought out, or else they led to reflex tonic contraction. Tickling the sole of the tremulous foot will, instead of producing a twitch of the leg, simply produce a cessation of the tremor, with or without a slight tonic contraction of the flexors. The cremasteric reflex is very prolonged, the trunk reflexes are lost.

To summarize now what I have gone over, I would say that paralysis agitans is characterized by a central vascularization of the spinal cord, a diffuse interstitial sclerosis starting from the blood-vessels and pia. This affects in particular the central and anterior portions of the gray matter and the lateral columns, leading in later stages to cell degeneration, leptomeningitis, and some peripheral sclerosis; that there is sometimes degenerative neuritis of the peripheral nerves and chronic myositis; that the cerebral cortex and the basal ganglia and the cerebellum, and, in fact, the brain as a whole, is but slightly and only secondarily involved; that this chronic irritative process is due to a toxine which circulates in the blood and may be of an endogenous and perhaps glandular origin; that the disease process first affects the end brushes surrounding the anterior horns and causes their degeneration; and that it finally impairs the anatomical structure of the motor and vasomotor-secretory cells, causing degeneration and atrophy of them to some extent.

THERAPEUTICAL.

After so much that is purely scientific, and perhaps purely hypothetical, I ought perhaps to say a word that may be interpreted as having a practical bearing upon the therapeutics of the disease. Paralysis agitans seems to me to be a disease whose progress at least we ought to stop, and which, in its early stages, we ought to cure. It is indeed with a feeling of humiliation that I watch the steadily downward progress of this painful malady in so many cases. There is no serious anatomical change at the basis

of this trouble, such as we find in chronic myelitis, or in tumors, or even in locomotor ataxia. There is nothing which makes it intrinsically improbable or impossible that we should cure this dire and painful malady. When we reflect upon the enormous achievements of the human intellect in other fields in erecting extraordinary specimens of engineering skill, in unfolding the wonderful powers of electricity, in organizing industry, and subduing every force of Nature to our use and making them tend toward the increase of our comfort, the enlargement of our knowledge, and the greatness of our civilization, it does seem pitiable that so small a problem as that of stopping the course of this apparently insignificant disease should be still unsolved. Is it because great and ingenious minds are not found in medicine, but are lured away by the fascinations of statecraft or the prizes of commerce? The line of inquiry of research should be, I think, pursued most diligently, most indefatigably, in this direction. If I am at all right in my theories of the disease, we must find some kind of antitoxine which will counteract the poison which circulates in the nervous centers, or we must, through some agent, stop this disordered action by which this poison is thrown into the system. Whether this can be done through any animal extracts, as has been done successfully with a still more serious malady as myxœdema, I do not know. In one typical case I had injections of brain juice made daily for a period of three weeks, but without any results whatever. While experimenting in this direction we must, of course, follow out as much as we can the symptomatic indications. These would lead us, for one thing, to order, as we all do, rest in the treatment of this disease. This is always indicated in irritative and inflammatory processes, and its usefulness in shaking palsy is acknowledged. After rest, I think it will be admitted that opium helps us most. Whether this is by dulling the sensory centers or by interfering with metabolic action or glandular activity, I can not say. I have found that the use of salicylate of sodium and of salol often secures excellent results, and this, too, I could only explain on the theory of some toxic substance or some diathetic poison being at the root of the symptoms.

Among the ancient remedies which were recommended in the disease is iron, and the fact which my examinations show, that in the later stages a chlorosis develops, would lead us to employ this in conjunction with arsenic. The older recommendations regarding severe counterirritation to the spinal cord might perhaps be wisely utilized in connection with our present knowledge of its pathology. I have myself seen good results follow from the application of counterirritation to the spinal cord. Of other remedies—such as hyoscine, eserine, strychnine, lukewarm baths—it is not necessary for me to speak. We are all familiar with their results and their disappointments.